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09/445,289	05/11/2000	GALINA V MUKAMOLOVA	49946-60261	9774

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EXAMINER

DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
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1645

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

09/445,289

Applicant(s)

MUKAMOLOVA ET AL.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 126-147 ~~is/are~~ are pending in the application.
- 4a) Of the above claim(s) 132-143 and 145-147 ~~is/are~~ are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 126-131 and 144 ~~is/are~~ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 August 2006 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 42400.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Preliminary Amendments

- 1) Acknowledgment is made of Applicants' preliminary amendments filed 10/27/06, 08/31/06, 05/04/04, 04/05/03, 10/22/02, 01/04/02, and 12/03/1999.

Election

- 2) Acknowledgment is made of Applicants' election filed 06/09/03 in response to the written lack of unity mailed 04/23/03. Applicants have elected invention I, claims 126-131 and 144, with traverse. Applicants' traversal is on the grounds that no lack of unity of invention rejection was made during the PCT phase of the corresponding international application. Applicants contend that all the claims are linked by a single, searchable, unifying aspect, i.e., the resuscitation of dormant, moribund or latent bacterial cells using a new class of bacterial cytokines or pheromones. Applicants cite MPEP 803 and state that the examination of the entire application on the merits will not result in a serious burden because all the claims will have substantial overlap. Applicants state that inventions I, II and III; inventions IV, V and VI; inventions VII, VIII and IX; and inventions X, XI and XII, have the same classification, and so also inventions VII, VIII and IX; and inventions X, XI and XII. Applicants ask that inventions I, II and III; inventions IV, V and VI; inventions VII, VIII and IX; and inventions X, XI and XII be rejoined into single groups.

Applicants' arguments have been carefully considered, but are not persuasive for the following reasons. First, the alleged single, searchable, unifying aspect, i.e., the resuscitation of dormant, moribund or latent bacterial cells using a new class of bacterial cytokines or pheromones, was known in the art at the time of the invention. See the art rejection set forth below. Second, the claims that are presented to this Office are different from the claims that were examined during the PCT phase of the corresponding international application. The current application is the national stage 371 application which contains multiple inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special

technical features. The expression 'special technical features' shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In the instant case, as set forth below under the art rejection(s), the first claimed method as well as the product that was used in the method of using the product for resuscitation of dormant, moribund or latent bacterial cells using the recited bacterial pheromone, was already disclosed in the art at the time of the invention. Thus, the special technical feature of the first claimed method does not define over the prior art. Although the product of invention IV, and the method of use of said product of invention I, is a permitted combination under PCT Rule 13.2, in the instant case, since the method of invention I or the product of invention IV is already disclosed in the art, the special technical feature is not a unifying feature. Technically, the absence of special technical feature permits the separation of the use of the product from the product itself. The special technical features of the second and third claimed inventions and the subsequently claimed inventions are delineated above. The methods of inventions II, III and VII through XII use products that do not share significant structure with each other or with the product used in the method of invention I. While the methods of inventions VII-IX use three different antibodies with three different immunospecificity, the methods of X-XII use three different nucleic acids that do not share significant structure with each other. The methods of inventions I-III use three different polypeptide sequences that do not share significant structure with each other, or with the products used in the methods of inventions VII-IX and inventions X-XII. A polypeptide is a single chain molecule which comprises amino acid residues. A nucleic acid molecule comprises purine and pyrimidine units. An antibody is a glycoprotein which includes IgG that comprises 2 heavy and 2 light chains containing constant and variable regions, including framework regions which act as a scaffold for the 6 complementarity determining regions (CDRs) that function to bind an epitope. A polypeptide is classified in class 530/350, a nucleic acid in class 536/23.7, and an antibody in class 530/387.9. Despite belonging to the same class/subclass, the products of inventions IV-VI do not share significant structure and require separate and individual searches for each of the sequence. Therefore, examining all the claims together, or inventions I, II and III; inventions IV, V and VI; inventions VII, VIII and IX; and inventions X, XI and XII would pose a serious search

and examination burden. For these reasons, the lack of unity held in the instant invention is proper and is hereby maintained.

Status of Claims

3) Claims 1-60 have been canceled via the preliminary amendment filed 12/02/1999.

Claims 61-80 have been added via the preliminary amendment filed 12/02/1999.

Claims 61-125 have been canceled via the preliminary amendment filed 04/05/2003.

New claims 126-147 have been added via the preliminary amendment filed 04/05/2003.

Claims 126-147 are pending.

Claims 132-143 and 145-147 have been withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Elected claims 126-131 and 144 are under examination. An Action on the Merits is issued for these claims.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' information disclosure statement filed 04/24/00. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Sequence Listing

5) Acknowledgment is made of Applicants' sequence listing filed 10/27/06, which has been entered on 11/10/06.

Priority

6) This application is a national stage 371 application of PCT/GB98/01619 filed 06/03/1998, which claims foreign priority to application 9711389.8 filed 06/04/1997 in United Kingdom and application 9811221.2 filed 05/27/1998.

It is noted that Applicants have submitted a certified copy of the foreign priority documents in this application.

Specification

7) The specification is objected to for the following reasons:

(a) The first paragraph does not provide the complete priority information as

indicated above under the section 'Priority'.

(b) At pages 39-44 of the instant specification, the references to the Figures are not sufficiently descriptive. The limitation 'Explanation of the Figures' at line 7 of page 39 of the specification should be replaced with the limitation 'Brief Description of the Drawings'. The limitation 'Figure 1' at line 9 of page 39 of the specification should be replaced with --Figures 1A to 1D--. The limitation 'Figure 2' at line 12 on page 40 of the specification should be replaced with --Figures 2A and 2B--. Similar amendments should be made to the rest of the Figure recitations wherever a Figure includes more than one panel. This should include Figures 3-9. Applicants should refer to these Figures accordingly throughout the specification.

(c) The use of the trademarks has been noted in this application. For example, see 'Mono Q' in paragraph bridging pages 40 and 41 as well as pages 46 and 47, pages 47, 49, 53 and 57; 'Tween-80' at line 6 of page 44; 'Sephadex' in paragraph bridging pages 46, 47, 56 and 57; and 'Sephadex' on page 55. The trademark recitations must be capitalized. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

(d) At least one amino acid sequence depicted in Figure 1D is inconsistent in structure or amino acid composition with the amino acid sequence presented in the substitute raw sequence listing filed 10/27/06. For example, the amino acid composition of SEQ ID NO: 27 in Figure 1D is not consistent with or the same as the amino acid composition of SEQ ID NO: 27 as depicted in the raw sequence listing filed 10/27/06. It is suggested that Applicants examine every sequence in the Figures and the specification to make sure that their composition is consistent with those listed in the raw sequence listing.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

8) Claims 126, 144 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 126 and 144 include the limitations: 'a polypeptide comprising at least 20% identity or homology with amino acid residues 117 to 184 of SEQ ID NO: 2' and 'a polypeptide homologue, allelic form, species variant or mutein comprising at least 50% identity or homology with amino acid residues 117 to 184 of SEQ ID NO: 2' respectively. Applicants state that support for the new claims can be found throughout the specification and claims, as originally filed, particularly in Figures 1 and 2. See page 7 of Applicants' amendment filed 04/05/03. However, there appears to be no descriptive support for a polypeptide having at least 20% or 50% identity or homology with 'amino acid residues 117 to 184 of SEQ ID NO: 2', or a polypeptide homologue, allelic form, species variant, or mutein thereof. There is no descriptive support for the claimed method for resuscitating dormant, moribund or latent bacterial cells comprising contacting bacterial cells with such a polypeptide, or a cell strain expressing a nucleic acid that encodes such a polypeptide. Therefore, the above-identified new limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F.2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed by pointing to specific lines and pages, for the new limitations, or alternatively, remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

9) Claims 126-131 and 144 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an *in vitro* method of resuscitating dormant cells of homologous *Micrococcus luteus* cells in LMM or stimulating the *in vitro* growth in Sauton medium of *Mycobacterium tuberculosis* H37Rv and stimulating the *in vitro* growth in broth E of *Mycobacterium smegmatis* and *Mycobacterium bovis* comprising contacting said cells with a purified Rp factor from *Micrococcus luteus* 'Fleming strain 2665' or NCIMB 13267 strain, does not reasonably provide enablement for an *in vivo* or *in vitro* method of resuscitating dormant, moribund, or latent cells of any bacteria comprising contacting said bacterial cells with an

isolated polypeptide comprising at least 20% or 50% identity or homology with residues 117 to 184 of SEQ ID NO: 2, a polypeptide homologue, allelic form, species variant, or mutein thereof, or with a cell strain that comprises a nucleic acid that encodes a polypeptide comprising at least 20% or 50% identity or homology with residues 117 to 184 of SEQ ID NO: 2, a polypeptide homologue, allelic form, species variant, or mutein thereof, and for a method wherein the recited polypeptide results in therapy, immunotherapy, prophylaxis, or diagnosis of any microbial infection, as claimed broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on the *Wands* factors. Factors to be considered in determining whether undue experimentation is needed are summarized therein. See also *Ex parte Forman*, 230 USPQ 546, 547 (BPAI 1986). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Circ. 1988) as follows:

- The amount of direction or guidance provided by the inventor(s);
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art;
- The breadth of the claims; and
- The quantity of experimentation necessary (time and expense) to make or use the invention based on the content of the disclosure.

In the instant case, the nature of the invention is a method for resuscitating dormant, moribund, or latent cells of any generic or unspecified bacteria comprising contacting said cells with an isolated polypeptide comprising at least 20% or 50% identity or homology with residues 117 to 184 of SEQ ID NO: 2 (i.e., a polypeptide variant of SEQ ID NO: 2), a polypeptide homologue, allelic form, species variant, or mutein thereof, or with a cell strain that comprises a nucleic acid that encodes a polypeptide comprising at least 20% or 50% identity or homology

with residues 117 to 184 of SEQ ID NO: 2, a polypeptide homologue, allelic form, species variant, or mutein thereof. The claimed method is not limited to an *in vitro* method, but encompasses an *in vivo* method. The term 'cell strain' in claim 144 encompasses a microbial cell, a prokaryotic, a eukaryotic cell etc. The limitation 'bacterial cells' encompasses all kinds of bacterial cells including pathogenic or highly virulent, drug-resistant, commensal, Gram negative and Gram positive, aerobic and anaerobic, fastidious and non-fastidious, and acid-fast bacterial cells. The method of claims 128 and 129 includes therapy or immunotherapy, prophylaxis, or diagnosis of any microbial infection. The limitation 'microbial infection' herein encompasses infections due to any microbe, including bacteria, fungi, parasites, viruses etc. A polypeptide comprising at least 20% or 50% identity or homology with amino residues 117 to 184 of SEQ ID NO: 2 is a polypeptide that has at least 80% or 50% non-identity or dissimilarity with amino residues 117 to 184 of SEQ ID NO: 2. This means that the polypeptide comprising at least 20% or 50% identity or homology with residues 117 to 184 of SEQ ID NO: 2, or a polypeptide homologue, allelic form, species variant, or mutein thereof as recited in the method of at least claims 128 and 129 is *required* to elicit therapeutic, immunotherapeutic, or prophylactic effects against infections due to any microbe, i.e., protect against, or eliminate or reduce morbidity and/or mortality due to any microbial infections, or have the capability to diagnose infections due to any microbe. However, a review of the instant specification reveals a lack of showing that contacting dormant, moribund, or latent cells of any bacteria, including *Micrococcus luteus*, with a polypeptide comprising 20% or 50% identity or homology with residues 117 to 184 of SEQ ID NO: 2, a polypeptide homologue, allelic form, species variant, or mutein thereof, or contacting with a cell strain comprising a nucleic acid expressing the same, does in fact bring about resuscitation of said bacterial cells *in vitro* or *in vivo*, let alone result in therapy, immunotherapy, prophylaxis, or diagnosis of any generic microbial infection. The disclosure however is enabling for an *in vitro* method of resuscitating dormant cells of homologous *Micrococcus luteus* cells in LMM (see Figures 4B and 7C) or stimulating the *in vitro* growth in Sauton medium of *Mycobacterium tuberculosis* H37Rv (see Figure 10) and stimulating the *in vitro* growth in broth E of *Mycobacterium smegmatis* and *Mycobacterium bovis* (see Figure 6) comprising contacting said cells with a purified Rp factor from *Micrococcus luteus* 'Fleming strain 2665' or NCIMB 13267 strain.

From Figure 1A and the description provided on page 50 of the specification, it appears that SEQ ID NO: 2 represents the predicted amino acid sequence of a polypeptide from 'MtubMTV008' obtained based on a BLAST search. From this description, it appears that SEQ ID NO: 2 is the amino acid sequence of a polypeptide of a *Mycobacterium tuberculosis*. However, it is recognized among those of skill in the art that assigning functional activities for any particular protein or a family of proteins based upon sequence homology is inaccurate, partly because of the multifunctional nature of proteins. See abstract; and page 34 of Skolnick *et al.* (*Trends in Biotechnology* 18: 34-39, 2000). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein. See abstract and Box 2 of Skolnick *et al.* In the instant application, the functions of the predicted mycobacterial gene product of SEQ ID NO: 2 found by genome sequencing projects are described to be 'unknown'. See first full paragraph in page 50 of the specification. This means that the functions of the polypeptide having at least 20% or 50% identity or homology with amino acid residues 117 to 184 of SEQ ID NO: 2, or a polypeptide homologue, allelic form, species variant, or mutein thereof is also 'unknown'. The instant specification at page 15 speculates that the localizing domain portion of a Rpf polypeptide 'may' confer important binding properties on the Rp-factor. There is no showing that even the unmodified or the full-length SEQ ID NO: 2 was tested for its ability to resuscitate dormant, moribund, or latent homologous bacterial cells, let alone any heterologous bacterial cells, or for its ability to be therapeutic, immunotherapeutic, or prophylactic against, or diagnostic of any microbial disease, including a disease due to the homologous *Mycobacterium tuberculosis*. In other words, no nexus is established between amino acid residues 117 to 184 of SEQ ID NO: 2, or a polypeptide homologue, allelic form, species variant, or mutein thereof and its ability to resuscitate the dormant, moribund or latent cells of any bacterial cells, or its therapeutic, immunotherapeutic, prophylactic, or diagnostic effects in homologous or any heterologous microbial infection. The RP factor purified from *Micrococcus luteus* 'Fleming strain 2665' or NCIMB 13267 strain is shown to strongly stimulate the *in vitro* growth of normal cells of *M. luteus* and *M. smegmatis*, and to have weaker activity on pathogenic mycobacteria, such as, *Mycobacterium tuberculosis*, *M. bovis*, and *M. avium*. See Figure 6 and

lines 9-14 on page 52 of the specification. The mycobacterial cells tested herein do not appear to be dormant, latent, or moribund. This however does not provide enabling disclosure for the method claimed in the instant claims wherein the recited polypeptide having at least 20% or 50% identity or homology (i.e., polypeptide variant) with amino acid residues 117 to 184 of SEQ ID NO: 2, or a polypeptide homologue, allelic form, species variant, or mutein thereof, is *required* to resuscitate dormant, moribund, or latent cells of any generically recited bacteria, or result in therapy, immunotherapy, prophylaxis, or diagnosis of any generic microbial infection. It should be noted that predictability or unpredictability is one of the *Wands* factors for enablement. With the function of the unmodified polypeptide being described in the specification as 'unknown', there is absolutely no predictability that the recited polypeptide variant having at least 80% or 50% non-identity or dissimilarity to amino acid residues 117 to 184 of SEQ ID NO: 2, or a polypeptide homologue, allelic form, species variant, or mutein thereof, is able to resuscitate dormant, latent, or moribund cells of any pathogenic or non-pathogenic bacteria, and result in therapy, immunotherapy, prophylaxis, or diagnosis of any generic microbial infection, including for example, a Gram negative bacterial infection, a fungal infection, a parasitic infection etc. In 1998, the art disclosed that genes encoding products comparably similar to Rpf are *not* present in any of the other organisms whose genomes have been completely or almost completely sequenced to date, including *Borrelia burrdorferi*, *E. coli*, *Haemophilus influenzae*, *Helicobacter pylori*, *Mycoplasma genitalium*, *Mycoplasma pneumoniae*, *Saccharomyces cerevisiae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Staphylococcus aureus* etc. See first full paragraph in right column on page 8920 of Mukamolova *et al.* *PNAS* 95: 8916-8921, July 1998 (Applicants' IDS). Lines 14-18 of page 5 of the specification state that heteroactive bacterial factors may act on eukaryotic cells including mammalian epithelial, endothelial, or immune cells. Such an action can be injurious to the host as opposed to be therapeutic or prophylactic. Other than disclosing the predicted structure of a polypeptide comprising SEQ ID NO: 2 having 'unknown' functions, the instant specification does not teach how to produce a polypeptide variant having at least 80% or 50% non-identity or dissimilarity to amino acid residues 117 to 184 of SEQ ID NO: 2, or a polypeptide homologue, allelic form, species variant, or mutein thereof, such that it is capable of resuscitating dormant, latent, or moribund cells of any pathogenic or non-pathogenic bacteria, or effecting therapy, immunotherapy, prophylaxis, or diagnosis of any generic microbial infection,

and how to use such a product *in vitro* or *in vivo* in the claimed method. There is no precise guidance in the instant specification with regard to which amino acid variations, i.e., insertions, deletions, additions, and/or substitutions, in the amino acid residues of 117 to 184 of the polypeptide of SEQ ID NO: 2 would result in a polypeptide variant of at least 20% or 50% identity or homology thereto, or a homologue, allelic form, species variant, or mutein thereof that would confer the ability to resuscitate dormant, latent, or moribund cells of any pathogenic or non-pathogenic bacteria, or the ability to effect therapy, immunotherapy, prophylaxis, or diagnosis of any generic microbial infection, without rendering it non-functional. This is important because the art reflects unpredictability as to which amino acids in a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional or biological properties of that specific protein. While it is known in the art that variation in one or more amino acids is possible in a given protein, the exact position within its amino acid sequence where replacements or variations can be made, with a reasonable expectation of success of retaining the protein's or polypeptide's functional competence, is not certain. The state of the art at the time of the invention, particularly with regard to unpredictability as associated with biologic functions of polypeptide variants reveals the following. The art shows that an alteration even in a single amino acid can eliminate or drastically change one or more function(s) of the polypeptide. With regard to polypeptides in general, Rudinger *et al.* (*In: Peptide Hormones*. (Ed) JA Parsons, University Park Press, pages 1-7, 1976) taught that 'the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study' (see page 6). Rudinger *et al.* further taught that 'it is impossible to attach a unique significance to any residue in a sequence' and that a 'given amino acid will not by any means have the same significance in different peptide sequences (i.e., fragments), or even in different positions of the same sequence (see page 3). The lack of guidance within the instant specification along with Rudinger's teachings further emphasize the unpredictability factor and the need to engage in considerable undue experimentation.

The instant specification at page 15 merely speculates that the localizing domain portion of a Rpf polypeptide 'may' confer important binding properties on the Rp-factor. How this assumed

or unsubstantiated binding properties influence therapy, immunotherapy, prophylaxis, or diagnosis of any 'microbial infection' via resuscitation of dormant, moribund, or latent cells of any 'bacteria' is unknown. The state of the art on microbial polypeptides in general indicates that a random replacement affecting the epitopic amino acid positions that are critical to the three-dimensional conformational structure and specific binding property of a protein, would result in a polypeptide that may be non-functional, or not optimally antigenic as a diagnostic reagent, or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines*86, Cold Spring Harbor Laboratory, p. 21-25, 1986) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively **unrecognizable** by any of the antibodies in the polyclonal pool. [Emphasis added]

The limitations 'therapy', 'immunotherapy', 'prophylaxis', or 'diagnosis' require that the recited polypeptide variant, homologue, or mutein is diagnostic, prophylactic, therapeutic, or immunotherapeutic in or against a generic 'microbial infection'. However, there is no evidence demonstrating this to be the case. For example, the limitation 'prophylaxis' requires that the recited polypeptide variant of at least 20% or 50% identity or homology, a homologue, allelic form, species variant, or mutein 'prevent' 'a microbial infection', for example, a *Mycobacterium tuberculosis* infection. The *Webster's II New Riverside University Dictionary* (1984) defines the term "prevent" as "to keep from happening". See page 933. Infection due to *M. tuberculosis* encompasses microbial cell invasion and growth or multiplication of the bacteria therein. The term 'infect' is defined in the illustrated *Stedman's Medical Dictionary* (24th Edition, Williams and Wilkins, London, 1982) as 'to enter, invade, inhabit, or to dwell internally'. See page 707. The specification does not enable a method wherein the recited polypeptide variant of at least 20% or 50% identity or homology, a homologue, allelic form, species variant, or mutein thereof keeps the process of tuberculosis infection from happening, prevents the entry and invasion of *M. tuberculosis* into a cell or its internal dwelling upon contacting the *M. tuberculosis* cells with the recited polypeptide variant of at least 20% or 50% identity or homology, a homologue, allelic

form, species variant, or mutein thereof. The specification lacks adequate guidance and disclosure that would limit the experimentation from being undue. The state of the art at the time of the invention was limited to certain unsubstantiated or unproven speculations with regard to the potential use of Rpf-like proteins in detection (or diagnosis), treatment, and prophylaxis. For instance, Mukamolova *et al.* (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al.*, 1998) stated that it was 'tempting to speculate' that resuscitation and growth of the very significant re-emerging pathogen *Mycobacterium tuberculosis* and possibly of *Mycobacterium leprae* 'may be' controlled in part at least by members of a family of secreted Rpf-like proteins that function as autocrine and/or paracrine growth factors. See last paragraph in left column on page 8921 of Mukamolova *et al.* (1998). In July 1998, Mukamolova *et al.* concluded as follows:

Further experimental work will be required to explore these hypotheses, which may lead, in the short term, to substantially improved laboratory methods for the detection and cultivation of these organisms and in the longer term, to therapeutic strategies and vaccines for preventing their growth *in vivo*.

Thus, neither the instant specification, nor the art at the time of the invention enabled the use of a polypeptide comprising SEQ ID NO: 2, let alone a fragment thereof comprising amino acid residues 117 to 184 of SEQ ID NO: 2, a homologue, allelic form, species variant, or mutein thereof, in therapy, immunotherapy, prophylaxis, or diagnosis of a single generic or specific microbial infection, which method includes the step of contacting dormant, moribund, or latent cells of a homologous or heterologous bacteria, with the isolated polypeptide comprising SEQ ID NO: 2, let alone a fragment thereof comprising amino acid residues 117 to 184 of SEQ ID NO: 2, a homologue, allelic form, species variant, or mutein thereof. Absent a concrete showing that the recited polypeptide having 20% or 50% identity or homology to amino acid residues 117 to 184 of SEQ ID NO: 2 (i.e., polypeptide variant), homologue, allelic form, species variant, or mutein thereof is capable of resuscitating dormant, moribund or latent cells of any bacteria and effecting therapy, immunotherapy, prophylaxis, or diagnosis of any microbial infection upon contacting it with bacterial cells, the claimed method is viewed as being non-enabled. Therefore, undue experimentation would have been required by one of skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific and adequate disclosure, the lack of working examples enabling the full scope, the art-demonstrated unpredictability, the quantity of experimentation necessary, and the breadth

of claims. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

10) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

11) Claims 126-131 and 144 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 126 and 144 are vague and indefinite in the recitation 'amino acid residues of SEQ ID NO:' without reciting that the recited SEQ ID NO: ... represents an amino acid sequence. For clarity and in order to distinctly claim the subject matter of the instant invention, it is suggested that Applicants replace the recitation with --amino acid residues of the amino acid sequence of SEQ ID NO:--.

(b) Claims 126 and 144 are vague and indefinite in the recitation 'homologue', 'species variant', or 'mutein', because it is unclear what is encompassed in these limitations. What constitutes a 'homologue', 'species variant', or 'mutein', and how much of the polypeptide's original structure has to be retained such that the resulting polypeptide can be considered as a 'homologue', 'species variant', or 'mutein', is not clear. The metes and bounds of the structure encompassed in the above-identified limitations are indeterminate.

(c) Claim 128 is confusing in the limitation: 'said polypeptide used in therapy, diagnosis, or prophylaxis of a microbial infection'. Is this using the polypeptide an additional step in addition to the contacting step recited in the base claim 126? Does it involve administering the recited polypeptide? It is unclear how contacting dormant, moribund, or latent 'bacterial cells' with the recited polypeptide and/or using the recited polypeptide can result in therapy, diagnosis, or prophylaxis of 'a microbial infection'. Clarification/correction is requested.

(d) Claim 129 is vague and indefinite in the phrase: 'therapy is immunotherapy'. Claim 129 depends directly from claim 128 and indirectly from claim 126. It is unclear how

contacting and/or the recited polypeptide with dormant, moribund, or latent 'bacterial cells' results in 'immunotherapy' of a microbial infection.

(e) Claim 129 is vague and indefinite in the phrase: 'strain expressing a nucleic acid encoding', because it is unclear what are Applicants trying to convey. It is unclear whether what is being expressed is polypeptide or nucleic acid.

(f) Claims 127-131, which depend from claim 126, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

12) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13) Claims 126, 127, 130, 131 and 144 are rejected under 35 U.S.C. § 102(a) as being anticipated by of Mukamolova *et al.* (*Arch. Microbiol.* 172: 9-14, July 1999) (Mukamolova *et al.*, 1999) as evidenced by Mukamolova *et al.* (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al.*, 1998).

Instant claims are granted the effective filing date of the instant application, i.e., 05/11/00 due to the new matter identified above. Therefore, the reference of Mukamolova *et al.* (1999) qualifies as prior art under 35 U.S.C. § 102(a).

Mukamolova *et al.* (1999) taught a method of resuscitating dormant cells of the 'Fleming strain 2665' of *Micrococcus luteus* comprising contacting said cells with an isolated proteinaceous growth factor, Rpf, or cells expressing Rpf. The Rpf was contained in a sterile-filtered culture supernatant, i.e., a pharmaceutically acceptable carrier suitable for local or systemic administration. See abstract; Materials and methods; Results; Tables 1-3; and Figures 2, 3 and 5. The strain of viable and dormant *Micrococcus luteus* used by Mukamolova *et al.* (1999) is the 'Fleming strain 2665' or NCIMB 13267 strain. See title; abstract; Materials and methods; Results; and Figure 2. The prior art 'Fleming strain 2665' of *Micrococcus luteus* is the very same strain

used in the instant invention by Applicants (see last paragraph on page 44 of the instant application), and therefore, the prior art strain is expected to necessarily comprise a nucleic acid that encodes the recited polypeptide homologue. Because the 'Fleming strain 2665' strain of *Micrococcus luteus* is the very same strain used in the instant invention by Applicants, the cells of this strain and the supernatant isolated from its culture are expected to necessarily secrete or express a homologue of the instantly recited polypeptide comprising amino acid residues 117 to 184 of SEQ ID NO: 2. That the prior art culture supernatant necessarily comprises a homologue of the instantly recited polypeptide comprising amino acid residues 117 to 184 of SEQ ID NO: 2 in a unit dosage form is inherent from the teachings of Mukamolova *et al.* (1999) in light of what is known in the art. For instance, Mukamolova *et al.* (1998) teach that the culture supernatant of the viable cells of the 'Fleming strain 2665' of *Micrococcus luteus* contains or secretes a proteinaceous resuscitation promoting factor that comprises the instantly recited amino acid residues 117 to 184 of SEQ ID NO: 2 and promotes the resuscitation and growth of dormant cells of the homologous organism in picogram quantities. See abstract; Materials and Methods; Results; and Figures 2 and 3 of Mukamolova *et al.* (1998).

The limitation 'recombinant' in claim 127 represents a process limitation. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case, Applicants have not shown the underlying structure of the prior art polypeptide differs from that of the instantly recited polypeptide.

Claims 126, 127, 130, 131 and 144 are anticipated by of Mukamolova *et al.* (1999). The reference of Mukamolova *et al.* (1998) is **not** used as a secondary reference in combination with Mukamolova *et al.* (1999), but rather is used to show that every element of the claimed subject

matter is disclosed by Mukamolova *et al.* (1999) with the unrecited characteristics being inherent therein. See *In re Samour* 197 USPQ 1 (CCPA 1978).

14) Claims 126, 127, 130, 131 and 144 are rejected under 35 U.S.C. § 102(b) as being anticipated by of Mukamolova *et al.* (*Antonie van Leeuwenhoek* 67: 289-295, 1995) (Mukamolova *et al.*, 1995) as evidenced by Mukamolova *et al.* (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al.*, 1998).

Mukamolova *et al.* (1995) taught a method of resuscitation of starved or dormant cells in *Micrococcus luteus* stationary cultures by contacting the dormant cells with a sterile-filtered supernatant isolated from the late log phase of viable cultures of the same *Micrococcus luteus* which supernatant contains an antibacterial factor secreted or expressed by the *Micrococcus luteus* cells, or by contacting with the resuscitating cells of *Micrococcus luteus* secreting or expressing an antibacterial factor. The sterile supernatant is contained in a minimal medium, i.e., a pharmaceutically acceptable carrier suitable for local or systemic administration. The strain of viable and dormant *Micrococcus luteus* used by Mukamolova *et al.* (1995) is the 'Fleming strain 2665' or NCIMB 13267 strain. See title; abstract; Materials and methods; Results; and Figure 2. The prior art 'Fleming strain 2665' of *Micrococcus luteus* is the very same strain used in the instant invention by Applicants (see last paragraph on page 44 of the instant application), and therefore, the prior art strain is expected to necessarily comprise a nucleic acid that encodes a homologue of the recited polypeptide. Because the 'Fleming strain 2665' strain of *Micrococcus luteus* is the very same strain used in the instant invention by Applicants, the cells of this strain and the supernatant isolated from its culture are expected to necessarily secrete or express a homologue of the instantly recited polypeptide comprising amino acid residues 117 to 184 of SEQ ID NO: 2. That the prior art culture supernatant necessarily comprises a homologue of the instantly recited polypeptide comprising amino acid residues 117 to 184 of SEQ ID NO: 2 in a unit dosage form is inherent from the teachings of Mukamolova *et al.* (1995) in light of what is known in the art. For instance, Mukamolova *et al.* (1998) teach that the culture supernatant of the viable cells of the 'Fleming strain 2665' of *Micrococcus luteus* contains or secretes a proteinaceous resuscitation promoting factor that comprises the instantly recited amino acid residues 117 to 184 of SEQ ID NO: 2 and promotes the resuscitation and growth of dormant cells of the homologous organism in

picogram quantities. See abstract; Materials and Methods; Results; and Figures 2 and 3 of Mukamolova *et al.* (1998).

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A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case, Applicants have not shown the underlying structure of the prior art polypeptide differs from that of the instantly recited polypeptide.

Claims 126, 127, 130, 131 and 144 are anticipated by of Mukamolova *et al.* (1995). The reference of Mukamolova *et al.* (1998) is **not** used as a secondary reference in combination with Mukamolova *et al.* (1995), but rather is used to show that every element of the claimed subject matter is disclosed by Mukamolova *et al.* (1995) with the unrecited characteristics being inherent therein. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Objection(s)

15) Claim 126 and those claims that depend therefrom and claim 144 are objected to for including non-elected subject matter, i.e., SEQ ID NO: 11 and SEQ ID NO: 43.

Remarks

16) Claims 126-131 and 144 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

18) Information regarding the status of an application may be obtained from the Patent

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Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

January, 2007


S. DEVI, PH.D.
PRIMARY EXAMINER